Detection of Residual Solvents in a Large-Molecule API by \(^1\)H NMR Spectroscopy

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Overview

The determination of residual solvents in an API by headspace GC-MS often requires the performance of multiple analyses, particularly when the potential residual solvents are numerous and diverse. In this study, a more rapid approach was taken to determine the solvents in a particular large-molecule API. A one-pulse CPMG pulse sequence was used to distinguish the signals of solvents from the large-molecule API signal. The robustness of the method was determined by varying multiple acquisition and processing parameters. The method requires the use of a single API sample and a single solvent reference sample.

Comparison of NMR Method to USP Method

Specific solvents of interest were analyzed for this study. Of the solvents used, four are Class 2 and five are Class 3. Sibling is not listed in the USP, and a separate method would be required for the high-molecular weight signal. A summary of the comparison between the two methods is provided below.

NMR Spectroscopy

- 50 g/mL API used
- Single standard and sample preparation
- Total analysis time of 4 minutes
- Use a more intense signal by 0.5 T-1 NMR on the same sample at the same time

Considerations for the NMR Method

Preparation of Assay Solution

- Single preparation to reduce weighing inaccuracies
- Verify purity, or a single time prior to preparation of solvent mix

Preparation of Sample for NMR Analysis

- Recrystallization of API and assay solvent
- Solubility of API in the required time

Acquisition and Processing of \(^1\)H NMR Spectrum

- 500 MHz Varian UNITY INOVA spectrometer
- T1 and T2 relaxation times were determined at ambient conditions (Figure 4).

Experiments and Optimization

- Optimization of CPMG Experiment
- T1 and T2 experiments were performed on a sample of API in DMSO-d\(_6\) to determine the relaxation behavior of the molecules of interest (Figure 6).

Signal Determination and Experiment Optimization

- Optimization of CPMG Experiment
- T1 and T2 experiments were performed on a sample of API in DMSO-d\(_6\) to determine the relaxation behavior of the molecules of interest (Figure 4). A series of spectra with differing delays were acquired, and the resulting spectra were compared. For each of the components, at least T1 and T2 relaxation delays were used.

Conclusion

- The method meets the requirement of specificity.
- Limit of Quantification
- A sample of API was prepared with each solvent present at 0.5% weight percent. The sample was analyzed by NMR as per the NMR method. The signal arising from the methylpropanol peak could be easily distinguished from the signal arising from the peak of interest. The solvent was used at a ratio of 1:10 for all solvents.

Intermediate Precision and Robustness

- The robustness of the method was determined by varying multiple acquisition and processing parameters. To test the robustness of the NMR spectra, the sample was spiked with 0.05% of the test solvents. The resulting signals were compared to the spectrum of the spiked sample, the API is considered to have no more than 0.05% residual solvent.

- The method meets the requirement for robustness.

Conclusions

- We have described the development and validation of a residual solvents limits test by NMR that is easy to execute on a routine basis with good sensitivity.
- The method meets the requirement for robustness.
- The method meets the requirement for linearity.
- The method meets the requirement for intermediate precision.